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Phase I study of BCX1777 (forodesine) in patients with relapsed or refractory peripheral T/natural killer-cell malignancies

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BCX1777 (forodesine), a novel purine nucleoside phosphorylase inhibitor, induces apoptosis, mainly in T cells. To evaluate the safety, tolerability, and pharmacokinetics of BCX1777, we conducted a phase I study in patients with relapsed or refractory peripheral T/natural killer-cell malignancies. Eligible patients had relapsed or refractory peripheral T/natural killer-cell malignancies without any major organ dysfunction. BCX1777 was administered orally once daily (dose escalation: 100, 200, and 300 mg) until disease progression requiring new therapy or unacceptable adverse events occurred. A total of 13 patients were enrolled and treated in three dose cohorts (100 mg/day, five patients; 200 mg/day, three patients; 300 mg/day, five patients). Although none of the patients developed dose-limiting toxicities, further dose escalation was not performed based on data from overseas. Therefore, the maximum tolerated dose was not determined. Adverse events of grade 3 or greater (≥2 patients) included lymphopenia (62%), anemia (15%), leukopenia (8%), and pyrexia (8%). Plasma pharmacokinetics parameter of BCX1777 (area under the plasma concentration-time curve) at day 1 in each cohort was 1948 ± 884, 4608 ± 1030, and 4596 ± 939 ng•h/mL, respectively. Disease control was achieved in approximately half of patients. One patient with anaplastic large cell lymphoma, which was negative for anaplastic lymphoma kinase, achieved a complete response, and two patients with cutaneous T-cell lymphoma achieved partial responses. BCX1777 was well tolerated at doses up to 300 mg once daily and showed preliminary evidence of activity in relapsed or refractory peripheral T/natural killer-cell malignancies, warranting further investigation. (*Cancer Sci* 2012; 103: 1290–1295)

Because children born deficient in purine nucleoside phosphorylase (PNP) have a reduced T-cell count, it has been suggested that PNP may be a potential target for treatment of T-cell–mediated diseases.[1] BCX1777 (forodesine), a transition-state analog PNP inhibitor, belongs to a novel class of PNP inhibitors and is 100–1000 times more potent than existing PNP inhibitors. The inhibition of PNP increases 2′-deoxyguanosine (dGuo) concentration in plasma and T cells and leads to dGuo triphosphate accumulation in T cells, causing imbalanced 2′-deoxynucleotide pools and apoptosis. Because intracellular phosphorylation of dGuo by deoxycytidine kinase is upregulated in malignant T cells, BCX1777 is considered to selectively suppress T-cell proliferation and, thus, is expected to have therapeutic efficacy in T-cell–related diseases, including T-cell leukemia/lymphoma.

Both *in vitro* and *in vivo* preclinical pharmacologic studies have shown that BCX1777 inhibits T- and B-cell proliferation, and early clinical trials in acute lymphoblastic leukemia, cutaneous T-cell lymphoma (CTCL), and chronic lymphocytic leukemia have suggested its efficacy and safety.[2] Here, we report the results of a multicenter, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics (PK) of BCX1777 in patients with relapsed or peripheral refractory T-cell or natural killer (NK)-cell malignancies.

Material and methods

Study design and patients. This was a phase I multicenter, open-label, dose-escalation study comprising a 14-day screening period, treatment period, and 30-day safety follow-up period.

Eligible patients had histologically confirmed relapsed or refractory peripheral T/NK-cell malignancies (excluding T-cell acute lymphocytic leukemia and T-cell lymphoblastic lymphoma), previous treatment with anticancer agents, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, adequate hepatic and renal function (alanine/aspartate aminotransferase ≤ 5 times upper limit of normal, creatinine clearance using Cockroft–Gault formula ≥ 50 mL/min), and were aged ≥ 20 years. Patients with $\leq 25\%$ malignant cells in their bone marrow had to have a neutrophil count $\geq 1200/mm^3$ and platelet count $\geq 75\ 000/mm^3$. Patients with CTCL (mycosis fungoides) were assumed to have $\leq 25\%$ malignant cells in their bone marrow.

Exclusion criteria included women known or suspected to be pregnant; serious infection; severe cardiovascular disease; treatment with other investigational drugs within 30 days or with other chemotherapeutic agents within 21 days before study treatment initiation; inability to take oral medication; being positive for hepatitis B surface antigen, hepatitis C virus antibody, HIV antibody, or cytomegalovirus antigen (by antigenemia assay); and/or central nervous system involvement requiring treatment.

Investigational drug. BCX1777 is manufactured by Mundipharma Research Limited (Cambridge, UK). Each capsule contains 100-mg forodesine. BCX1777 was orally administered once daily after breakfast until disease progression requiring new therapy or unacceptable adverse events (AE) occurred. During the treatment period, patients were followed for safety and response. The daily dose was increased stepwise from 100 mg (cohort 1) to 200 mg (cohort 2) to 300 mg (cohort 3), and three or more patients were assigned to each cohort. The

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starting dose and schedule were based on information from a previous clinical trial.[3] The decision to proceed from one cohort to the next was based on the safety data from the first three patients who received BCX1777 in the present cohort for 28 days. If none of the first three patients experienced dose-limiting toxicity (DLT) in the first 28 days of treatment, three or more subsequent patients were enrolled in the next cohort. In contrast, if all of the first three patients experienced DLT, no further escalation was permitted. If one or two of the first three patients experienced DLT, up to three additional patients were enrolled in the present cohort, and if the number of patients experiencing DLT remained at one or two, three or more subsequent patients were enrolled in the next cohort. However, if there were no more than six patients and at least three experienced DLT, no further escalation was permitted. Concomitant use of other anticancer agents, corticosteroids to control the primary disease or conditions related to the primary disease, and prophylactic use of hematopoietic growth factors were not permitted. Patients were allowed to receive anti-emetics, antidiarrheals, and erythropoietin at the physician's discretion, and they were able to receive prophylactic sulfamethoxazole-trimethoprim and anti-herpesvirus drugs. Patients with cytomegalovirus reactivation were allowed to receive anti-cytomegalovirus therapy if medically indicated.

Safety assessments. Safety assessments included AE, serious AE (death, life-threatening AE, hospitalization, disability, or permanent damage), laboratory tests, vital signs, body weight, 12-lead electrocardiograms, and ECOG PS.

Treatment-emergent AE were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, and were summarized by preferred term in the Medical Dictionary for Regulatory Activities, version 12.0.

We defined DLT as any AE that occurred $\leq$28 days after the start of BCX1777 treatment that was considered related to the treatment and met the following criteria: (i) grade 3/4 non-hematologic toxicity (excluding nausea, vomiting, and diarrhea); (ii) grade 4 neutropenia or thrombocytopenia (including that requiring platelet transfusion) for patients with $\leq$25% malignant cells in the bone marrow at screening (patients with CTCL were assumed to have $\leq$25% malignant cells in the bone marrow); and (iii) grade 4 neutropenia or thrombocytopenia (including that requiring platelet transfusion) lasting for $\geq$7 days for patients with >25% malignant cells in the bone marrow at screening.

Pharmacokinetic assessments. For PK analysis, BCX1777 plasma concentrations were determined by liquid chromatography/tandem mass spectrometry. Blood samples were collected at 0, 1, 2, 4, 6, and 8 h after dosing on days 1 and 15, and at 0 h after dosing on days 2, 3, 4, 8, 16, 29, and 57.

Plasma PK parameters, including peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), and area under the plasma concentration-time curve (AUC), were calculated for each patient on days 1 and 15, with individual plasma BCX1777 concentration data from noncompartmental analysis and summarized by dose cohort. On days 1 and 15, C_{max} and AUC were tested for dose proportionality with a linear regression model and a power model.

Pharmacodynamic assessments. BCX1777 pharmacodynamics were assessed by examining the change in plasma dGuo concentrations. Blood samples for plasma dGuo analysis were collected at the same time points as for the BCX1777 PK analysis. Plasma dGuo concentrations were determined by liquid chromatography/tandem mass spectrometry; plasma dGuo parameters were analyzed in the same manner as the plasma BCX1777 PK parameters.

Efficacy assessments. The efficacy endpoint was objective tumor response. Clinical response was assessed on day 57 and every 8 weeks thereafter. Response was evaluated according to International Workshop Criteria (1999) for lymphoma.[4] For CTCL, response was evaluated based on modified severity-weighted assessment tool score and lymph node assessment.[5]

Study conduct and patient consent. This study was conducted in compliance with the 2008 Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines protocol. It was approved by the institutional review board at each participating center, and all patients provided written informed consent before study participation.

Results

Patient characteristics. A total of 13 patients were enrolled and received study treatment: five at 100 mg once daily (cohort 1), three at 200 mg once daily (cohort 2), and five at 300 mg once daily (cohort 3). Of these, four patients discontinued treatment during the 28-day DLT evaluation period (two at 100 mg once daily, two at 300 mg once daily). The reasons for treatment discontinuation were "disease progression requiring new therapy" for three patients and "investigator's judgment" for one patient. The treatment of the latter patient was discontinued after computed tomography indicated disease progression. It was later determined that the shadow was derived from cytomegalovirus infection. No patients discontinued the protocol treatment because of DLT during the 28-day period. The remaining nine patients continued study treatment (three per cohort). At the time of data cutoff (2010 February 15, the date when the last enrolled patient completed 16 weeks of follow-up), two patients were still receiving study treatment (one at 100 mg once daily, one at 300 mg once daily). Of the seven patients who discontinued study treatment after day 29, the reasons for treatment discontinuation were "disease progression requiring new therapy" for six patients and "grade 3 nonhematologic toxicity (viral infection)" for one patient.

The study population characteristics are shown in Table 1. The study population was mostly men (62%), with a median age of 69 years. The most common diagnosis was peripheral T-cell lymphoma (PTCL)-not otherwise specified, followed by anaplastic lymphoma kinase-negative anaplastic large cell lymphoma (ALCL), CTCL (mycosis fungoides), and primary cutaneous ALCL. The most common stage of lymphoma was IIIA, and 11 patients (85%) had an ECOG PS of 0. Excluding the two patients with CTCL who had no bone marrow examination, the percentage of malignant cells in the bone marrow was $\leq$25% in all 11 patients. The mean medication adherence rate in each cohort was 97–99%.

Safety. The median (minimum, maximum) duration of treatment was 111 (9, 337) days for all patients and 35 (9, 337), 168 (121, 205), and 28 (15, 116) days for those who received 100, 200, and 300 mg, respectively. All patients were included in the safety analysis. AE recorded in this study are summarized in Table 2. No deaths were reported. Serious AE occurred in two patients: one patient receiving 100-mg BCX1777 developed herpes zoster on day 100 and a viral infection of unknown pathogen on day 166, and another patient receiving 200-mg BCX1777 developed cellulitis on day 157. The viral infection was grade 3 and led to treatment discontinuation. No AE required dose reduction. Furthermore, no DLT were observed during the first 28 days of study treatment. One AE requiring treatment interruption occurred in the patient receiving 100-mg BCX1777 (the same patient with a viral infection and herpes zoster). The patient developed upper respiratory tract inflammation related to BCX1777 on day 15, and treatment was temporarily interrupted at the discretion of the investigator. However, the AE was grade 2 in severity and did not correspond to a DLT.

All patients experienced AE. Overall, 123 total AE were reported, the majority of which (100 events) were considered

Table 1. Patient characteristics

Characteristics	BCX1777			
	100 mg *n* = 5	200 mg *n* = 3	300 mg *n* = 5	All *N* = 13
Sex, *n* (%)				
Men	3 (60)	1 (33)	4 (80)	8 (62)
Women	2 (40)	2 (67)	1 (20)	5 (38)
Age, year				
Median (range)	56 (30–70)	60 (51–77)	71 (58–74)	69 (30–77)
Histopathologic subtypes, *n* (%)				
PTCL-NOS	2 (40)	0	4 (80)	6 (46)
ALK-negative ALCL	3 (60)	0	0	3 (23)
CTCL (MF)	0	2 (67)	0	2 (15)
C-ALCL	0	1 (33)	1 (20)	2 (15)
Stage† (CTCL), *n* (%)				
IIB	0	1 (33)	0	1 (8)
IVA	0	1 (33)	0	1 (8)
Stage‡ (PTCL-NOS, ALCL, C-ALCL), *n* (%)				
IA	1 (20)	0	0	1 (8)
IIA	1 (20)	1 (33)	1 (20)	3 (23)
IIIA	1 (20)	0	3 (60)	4 (31)
IIIB	1 (20)	0	0	1 (8)
IVA	1 (20)	0	1 (20)	2 (15)
Previous treatment: Number of chemotherapy regimens, *n* (%)				
1	1 (20)	2 (67)	1 (20)	4 (31)
2	1 (20)	1 (33)	2 (40)	4 (31)
3	0	0	0	0
≥ 4	3 (60)	0	2 (40)	5 (38)
Median (range)	6 (1–8)	1 (1–2)	2 (1–6)	2 (1–8)
Previous treatment: radiotherapy	1 (20)	3 (100)	1 (20)	5 (38)

†International Society for Cutaneous Lymphomas and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer criteria[6]. ‡Ann Arbor staging criteria. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; C-ALCL, primary cutaneous anaplastic large cell lymphoma; MF, mycosis fungoides; PTCL-NOS, peripheral T-cell lymphoma–not otherwise specified.

Table 2. Number of patients with adverse events (AE)

Type of AE	BCX1777		
	100 mg *n* = 5	200 mg *n* = 3	300 mg *n* = 5
AE, *n* (%)	5 (100)	3 (100)	5 (100)
Serious AE, *n* (%)	1 (20)	1 (33)	0
AE of grade ≥ 3, *n* (%)	4 (80)	2 (67)	3 (60)
AE leading to treatment discontinuation, *n* (%)	1 (20)	0	0
AE requiring treatment interruption or dose reduction, *n* (%)	1 (20)	0	0
Deaths, *n*	0	0	0

to be treatment related. No dose-related differences existed in number of AE.

The AE that occurred in at least two patients are listed in Table 3; these include AE of grade ≥ 3 including lymphopenia in eight patients (62%), anemia in two patients (15%), leukopenia in one patient (8%) and pyrexia in one patient (8%).

Table 3. Adverse events in at least two patients (*n* = 13)

Events, *n* (%)	Grade 1	Grade 2	Grade 3	Grade 4
Nasopharyngitis	2 (15)	0	0	0
Cancer pain	2 (15)	1 (8)	0	0
Anemia	2 (15)	0	1 (8)	1 (8)
Leukopenia	1 (8)	2 (15)	1 (8)	0
Lymphopenia	0	4 (31)	4 (31)	4 (31)
Neutropenia	0	3 (23)	0	0
Headache	2 (15)	0	0	0
Constipation	4 (31)	1 (8)	0	0
Nausea	3 (23)	0	0	0
Rash	2 (15)	3 (23)	0	0
Malaise	2 (15)	1 (8)	0	0
Edema peripheral	3 (23)	0	0	0
Pyrexia	0	1 (8)	1 (8)	0
Aspartate aminotransferase increased	2 (15)	0	0	0
Blood lactate dehydrogenase increased	5 (38)	0	0	0
Weight decreased	1 (8)	1 (8)	0	0

Pyrexia was judged as not related to treatment. Hematologic toxicities of grade ≥ 4 occurred in 5 of 13 patients (38%). Grade 4 lymphopenia occurred in two patients receiving 100-mg BCX1777 and two patients receiving 200-mg BCX1777. In one patient (J01-01-01) treated with BCX1777 for an extended period after data cutoff, grade 4 lymphopenia persisted during the treatment period. Grade 4 anemia occurred in one patient receiving 300-mg BCX1777. All grade 4 events were non-serious and were not DLT. No grade 5 event occurred.

Laboratory test results showed no remarkable changes until day 29, and no time-dependent changes. In addition to the grade $\geq$ 3 laboratory abnormalities (Table 3), one patient had a grade 3 thrombocytopenia.

Median baseline, nadir, and last dose lymphocyte counts (/μL) in all patients were 692, 351, and 504, respectively; median cluster of differentiation (CD) 4-positive cells (/μL) in all patients were also 223, 132, and 147, respectively.

Vital signs (blood pressure, pulse rate, and body temperature) and body weight showed no consistent changes during study treatment. No patients had new, clinically significant abnormal findings on 12-lead electrocardiograms.

Pharmacokinetics. The time courses of the mean plasma BCX1777 concentrations by dose cohort are shown in Figure 1(a). On day 1, mean plasma BCX1777 concentrations reached a peak at 4 h after dosing and then declined rapidly in all cohorts. Trough plasma BCX1777 concentrations were stable from days 2 to 15. Plasma BCX1777 concentrations after dosing on day 15 were higher than those on day 1 but followed a similar time course.

Plasma PK parameters of BCX1777 on days 1 and 15 by dose cohort are shown in Table 4. The T_{max} values were similar across doses on day 1 and on day 15; elimination half-life was also similar across doses as measured on day 1. On day 1, C_{max} and AUC increased with an increase in the BCX1777 dose from 100 to 200 mg, but they were similar at BCX1777 doses of 200 and 300 mg. As observed on day 1, C_{max} and AUC on day 15 increased with the increase in BCX1777 dose from 100 to 200 mg, but they were similar at BCX1777 doses of 200 and 300 mg. In the statistical assessment of the dose proportionality of C_{max} and AUC on days 1 and 15 using a power model, the estimates (95% confidence intervals) of the linear regression slope were 0.922 (0.390–1.454) and 0.784 (0.158–1.410) for C_{max} and 0.876 (0.438–1.314) and 0.769

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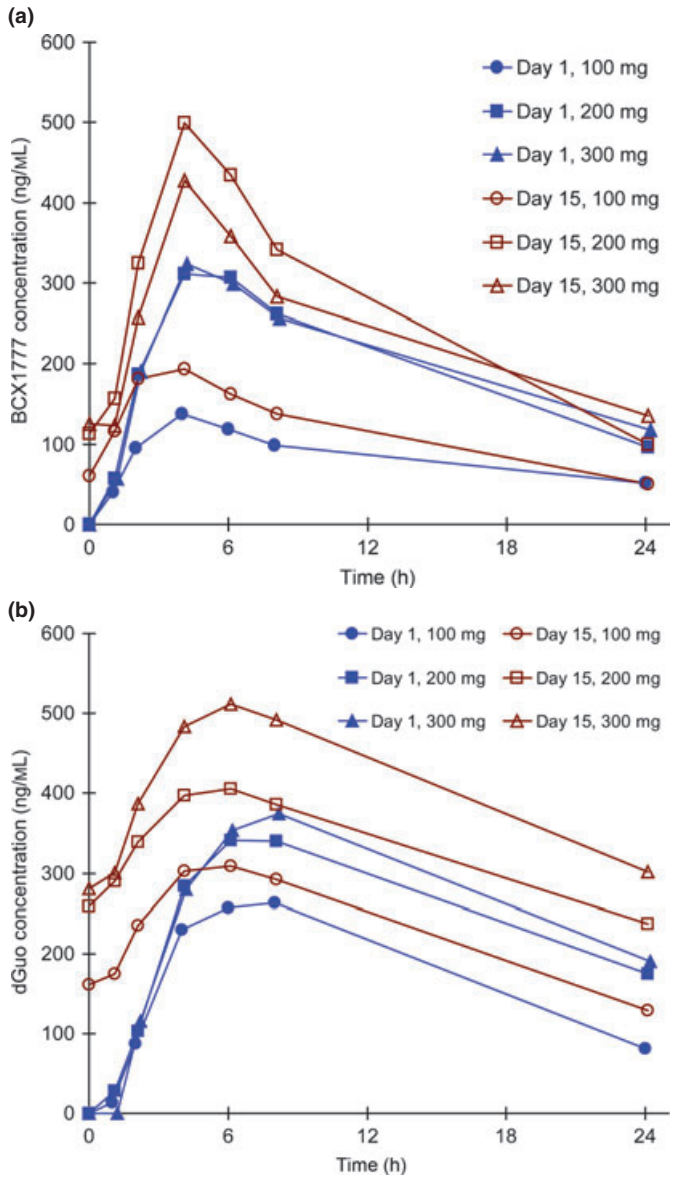

Fig. 1. Mean plasma concentrations after dosing of BCX1777. (a) BCX1777 and (b) 2′-deoxyguanosine (dGuo).

Table 5. Overall response assessment

BCX1777 dose	Patient number	Diagnosis	Best overall response	PFS
100 mg (n = 5)	J01-01-01†	ALK-negative ALCL	CR	331‡
	J01-03-01	PTCL-NOS	SD	120‡
	J01-03-02	PTCL-NOS	PD	17
	J01-03-03	ALK-negative ALCL	PD	35
	J01-04-02	ALK-negative ALCL	PD	9
200 mg (n = 3)	J01-01-02	CTCL	PR	169
	J01-02-02	C-ALCL	SD	122
	J01-03-04	CTCL	PR	113
300 mg (n = 5)	J01-02-03	PTCL-NOS	PD	29
	J01-03-05	PTCL-NOS	PD	25
	J01-03-06	PTCL-NOS	NE	NE
	J01-04-03	C-ALCL	SD	112
	J01-04-04	PTCL-NOS	PD	54

†As of October 2011, this patient is continuing BCX1777 therapy for >935 days. ‡Censored. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; C-ALCL, primary cutaneous anaplastic large cell lymphoma; CR, complete response; CTCL, cutaneous T-cell lymphoma; NE, not evaluable; NOS, not otherwise specified; PFS, progression-free survival; PD, progressive disease; PR, partial response; PTCL, peripheral T-cell lymphoma; SD, stable disease.

(0.241–1.297) for AUC on days 1 and 15, respectively. This may indicate that C_{max} and AUC on days 1 and 15 were dose proportional over the range of 100 to 300 mg because the 95% confidence intervals included 1.

Pharmacodynamics. On day 1, the mean plasma dGuo concentrations reached a peak at 6–8 h after dosing and then declined rapidly in all dose cohorts. Plasma dGuo concentrations that were determined before dosing increased on days 2 and 3 remained stable thereafter until day 15. Plasma dGuo concentrations after dosing on day 15 were higher than those on day 1 but followed a similar time course as on day 1 (Fig 1b).

Plasma dGuo parameters are shown in Table 4. Plasma dGuo C_{max} and AUC on days 1 and 15 increased with increasing doses of BCX1777, but T_{max} was similar at all doses. In contrast, in the statistical assessment of the dose proportionality of dGuo C_{max} and AUC on days 1 and 15 using a power

Table 4. Plasma PK parameters of BCX1777 and pharmacodynamic parameters of dGuo

BCX1777 dose	C_{max}, ng/mL		T_{max}, h		AUC, ng·h/mL		$t_{1/2}$, h
	Day 1	Day 15	Day 1	Day 15	Day 1†	Day 15‡	Day 1
Plasma PK parameters of BCX1777							
100 mg (day 1, n = 5 day 15, n = 4)	139.2 ± 83.1	216.5 ± 136.2	8.1 ± 8.2	4.1 ± 1.7	1948 ± 884	2730 ± 1358	13.0 ± 3.8
200 mg (n = 3)	335.3 ± 106.2	499.0 ± 155.9	4.0 ± 2.0	3.9 ± 0.1	4608 ± 1030	6303 ± 1052	14.1 ± 10.3
300 mg (n = 5)	328.0 ± 64.0	421.6 ± 49.6	4.3 ± 0.8	4.0 ± 0.1	4596 ± 939	5587 ± 920	14.4 ± 6.8
Pharmacodynamic parameters of dGuo							
100 mg (day 1, n = 5 day 15, n = 4)	270.4 ± 66.8	315.5 ± 49.2	6.6 ± 1.7	5.0 ± 1.2	4023 ± 1101	5384 ± 981	—
200 mg (n = 3)	348.7 ± 48.0	410.7 ± 103.9	7.3 ± 1.3	4.6 ± 1.2	5705 ± 571	7696 ± 2051	—
300 mg (n = 5)	374.4 ± 67.4	515.8 ± 116.2	7.6 ± 0.5	5.6 ± 0.8	6074 ± 1230	9533 ± 2677	—

Each value represents mean ± standard deviation. BCX1777 PK parameters were calculated with measurable plasma BCX1777 concentrations (≥2.5 ng/mL [LLQ]). Pharmacodynamic plasma dGuo parameters were calculated with measurable plasma dGuo concentrations (≥5.0 ng/mL [LLQ]). †AUC on day 1 was calculated from time 0 to 24 h. ‡AUC on day 15 is steady state AUC when tau is set at 24 h. AUC, area under the concentration-time curve; C_{max}, peak plasma concentration; dGuo, 2′-deoxyguanosine; LLQ, lower limit of quantification; PK, pharmacokinetics; $t_{1/2}$, terminal half-life; T_{max}, time to peak plasma concentration.

model, the upper limits of 95% confidence intervals of the linear regression slope were all <1, which may suggest that there was no dose proportionality.

Treatment response. Overall response assessment is shown in Table 5. There was complete response in one patient and partial response in two patients. In addition, three patients had stable disease.

Discussion

Although first-line treatment with potent chemotherapeutic agents improves patient outcome, T-cell leukemia/lymphoma is generally treatment resistant, and relapsed or refractory disease is associated with poor prognosis.[7–10] Novel anticancer agents are needed to expand drug treatment options. The antifolate pralatrexate was approved for PTCL treatment,[11] and denileukin diftitox and the histone deacetylase inhibitors vorinostat and romidepsin were approved for treatment of CTCL by the US Food and Drug Administration.[5,12–14] Anti-C-C chemokine receptor type 4 (CCR4) antibody is now under development for treatment of PTCL, CTCL, and adult T-cell leukemia-lymphoma (ATL).[15]

The study presented here is the first multicenter phase I study of BCX1777 involving patients with relapsed or refractory peripheral T/NK-cell malignancies, including PTCL. Most AE were considered treatment related, and there were no differences in the incidence between dose cohorts. Furthermore, because no DLT were observed at the highest BCX1777 dose in three patients, the maximum tolerated dose of BCX1777 could not be established. Further dose escalation was not performed as a result of the sponsor's decision, which was based on data from the US. This data indicated that the maximum tolerated dose of BCX1777 was not achieved at doses far higher than those used in the current study,[3] and other, unpublished data indicated that doses greater than 300 mg/day did not produce a significant increase in AUC. Our further, preliminary investigations in healthy volunteers suggest that dosing frequency is important in determining the maximum tolerated dose of BCX1777, and as such, dosing frequency must be examined in greater depth in future studies.

Serious AE included herpes zoster and viral infection in one patient receiving 100 mg/day and cellulitis in one patient receiving 200 mg/day. Resolution of the viral infection, which was grade 3 and led to study discontinuation, was confirmed at a follow-up visit after study completion. The cellulitis and herpes zoster were grade 2 and resolved with antimicrobial or antiviral therapy. Because these serious AE occurred in the context of grade 4 lymphopenia, it cannot be ruled out that BCX1777–induced lymphopenia may have compromised the immune system and caused these infectious events. Analysis of peripheral blood mononuclear cells expressing surface markers (CD3, CD4, CD8, CD16, CD20, and CD56) showed no marked reduction in specific subsets, and lymphocytes, as a whole, appeared to gradually decrease during study treatment (data not shown).

Once-daily oral BCX1777 was well tolerated at all doses. As suggested by previous studies,[2,3] the results are consistent with the idea that, unlike other nucleic acid analogs including fludarabine, cladribine, and cytarabine, BCX1777 is unlikely to cause myelosuppression, mucositis, and hair loss because it does not undergo intracellular phosphorylation and, therefore, is not incorporated into newly synthesized DNA.

Plasma BCX1777 concentrations reached a peak at 4 h after oral dosing and then declined rapidly. The steady state appeared to be reached by day 2 because trough plasma BCX1777 concentrations were stable on days 2–15. Plasma C_{max} and AUC of BCX1777 increased with the increase in dose from 100 to 200 mg/day but were similar at 200 and 300 mg/day on days 1 and 15. Further statistical assessments suggested that dose proportionality of C_{max} and AUC may also be present at up to 300 mg/day, but this was not firmly established.

Plasma dGuo concentrations reached a peak at 6–8 h after dosing and then declined rapidly, showing a similar time course to that of plasma BCX1777 concentrations. Trough plasma dGuo concentrations increased on days 2 and 3, and remained stable thereafter, suggesting that steady state dGuo concentrations were reached by day 3 or 4.

Plasma dGuo C_{max} and AUC on days 1 and 15 increased with increasing doses of BCX1777, but T_{max} was similar at all doses and some suggestion of the lack of dose proportionality in dGuo C_{max} and AUC exists. The time course patterns of plasma BCX1777 and dGuo concentrations were similar to those observed in a US phase I/II study of BCX1777 in patients with relapsed or refractory CTCL.[3] However, the present study does not provide conclusive evidence for the relationship among PK parameters (plasma BCX1777 C_{max} and AUC on days 1 and 15), pharmacodynamic parameters (plasma dGuo C_{max} and AUC on days 1 and 15), and dose of BCX1777 because of the limited number of enrolled patients.

The preliminary evidence presented here shows that about half the patients achieved disease control. These preliminary data suggest BCX1777 activity in relapsed or refractory peripheral T/NK-cell malignancies. One patient with anaplastic lymphoma kinase-negative ALCL achieved complete response, and both patients with CTCL (mycosis fungoides) achieved partial response. The anaplastic lymphoma kinase-negative ALCL patient is still in complete response and has been receiving BCX1777 for >935 days (as of October 2011), more than 1 year after the date of data cutoff. The study, however, was too small to compare BCX1777 efficacy in different lymphoma subtypes and did not include patients with ATL or T/NK-cell lymphoma.

In summary, the results of this phase I trial showed that BCX1777 was well tolerated at all dose levels tested in patients with relapsed or refractory peripheral T/NK-cell malignancies, including PTCL and CTCL. The preliminary evidence of antitumor activity, in addition to good tolerability, warrants further investigation including a single-agent phase II study or combination study with other agents in patients with peripheral T/NK-cell malignancies.

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